STATISTICAL ANALYSIS PLAN

INCB 50465-202 / NCT02998476

A Phase 2, Multicenter, International, Open-Label, Safety and Efficacy Study of INCB050465 in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (CITADEL-202)

IND Number:	**121,474**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
BTK	Bruton's tyrosine kinase
CI	confidence interval
CL/F	oral dose clearance
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLBCL	diffuse large b-cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
IDMC	independent Data Monitoring Committee
IRC	independent Review Committee
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NMR	no metabolic response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival

Abbreviation	Term
[redacted]	[redacted]
PMD	progressive metabolic disease
PMR	partial metabolic response
PP	per protocol (population)
PR	partial response
PT	preferred term
QD	once daily
QTcF	Fridericia correction
QW	once weekly
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
V/F	volume of distribution
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, multicenter, international, open-label study designed to evaluate the safety and efficacy of INCB050465 20 mg QD for 8 weeks followed by 20 mg QW. The study drug will be administered orally to subjects with relapsed or refractory DLBCL. The study consists of 2 groups: Group A and Group B. In Group A, 100 subjects who were not previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. In Group B, up to 20 subjects who were previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled.

Section 1 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCB050465.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 50465-202 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee.

[redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 50465-202 Protocol Amendment 3 dated 23 FEB 2017 and CRFs approved 16 NOV 2017. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives

2.2.1. Primary Objective

- To assess the efficacy of INCB050465 in terms of ORR in subjects with relapsed or refractory DLBCL in Group A.

2.2.2. Secondary Objectives

- To assess the DOR in Group A.
- To assess PFS in Group A.
- To assess OS in Group A.
- To characterize the safety of INCB050465 in Group A and Group B.

[redacted]

2.3. Study Endpoints

2.3.1. Primary Endpoint

- ORR in Group A, defined as the percentage of subjects with a CR/CMR or PR/PMR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.

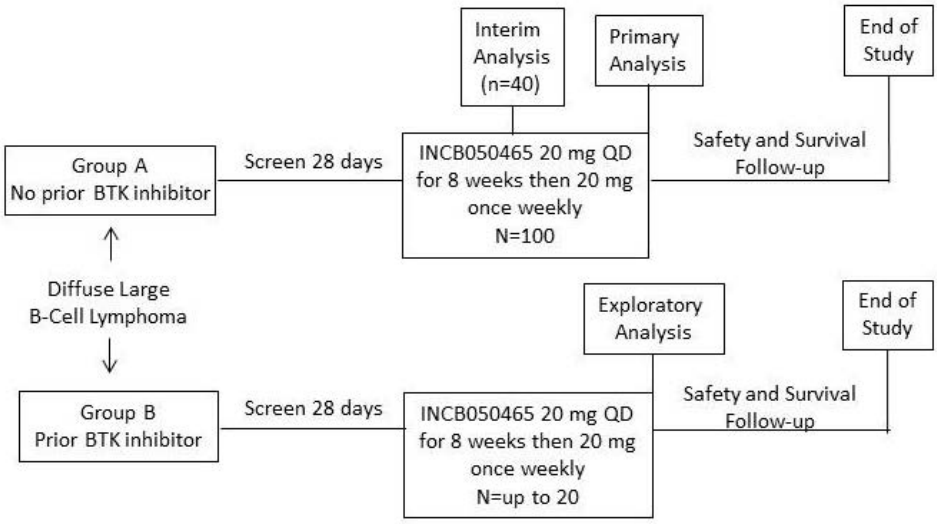
2.3.2. Secondary Endpoints

- DOR in Group A, defined as the time from first documented evidence of CR/CMR or PR/PMR until disease progression or death from any cause among subjects who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
- PFS in Group A, defined as the time from the date of the first dose of study drug until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
- OS in Group A, defined as the time from the date of the first dose of study drug until death by any cause.
- Safety as measured by clinical assessments, including vital signs and physical examinations, 12-lead ECG, chemistry and hematology laboratory values, and AEs.

3. STUDY DESIGN

This is a Phase 2, multicenter, international, open-label study designed to evaluate the safety and efficacy of INCB050465 20 mg QD for 8 weeks followed by 20 mg QW. The study drug will be administered orally to subjects with relapsed or refractory DLBCL (see Figure 1). The study consists of 2 groups: Group A and Group B. In Group A, 100 subjects who were not previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. In Group B, up to 20 subjects who were previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. Subjects will be evaluated for ORR by an IRC and followed for DOR, PFS, and OS. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal. An interim futility analysis is planned when the first 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if ≤ 13 of the 40 subjects have responded (ie, CR/CMR or PR/PMR) based on assessments provided by the IRC; otherwise the study will continue. No formal futility analysis will be conducted for Group B.

Figure 1: Study Design



3.1. Randomization

Not applicable.

3.2. Control of Type I Error

There will not be any statistical comparison between the 2 groups. Within each group, 2-sided 95% CIs will be reported for all analyses when appropriate.

Within each group, no adjustment for alpha-spending is considered, as there are no plans to stop the study early for overwhelming efficacy. An IDMC will be assembled to monitor safety data and study conduct on a regular and ongoing basis during the study. The IDMC will also be charged with evaluating interim futility results. See Section 9 for details regarding interim analyses conducted in this study.

3.3. Sample Size Considerations

The study will enroll 100 subjects into Group A. If the true ORR is 0.50, then there is approximately 90% probability of observing the lower bound of the 95% CI of the ORR ≥ 35%.

The study will enroll up to 20 subjects in Group B. [redacted]

3.4. Schedule of Assessments

Refer to Protocol Amendment 3 dated 23 FEB 2017 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study drug (INCB050465) is administered to the subjects.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of -1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCB050465, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

When calculating time since diagnosis/transformation of cancer, partial diagnosis/transformation date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the subject discontinued treatment.
- Otherwise, the date that the subject discontinued treatment will be used as the date of the last dose.

When calculating DOR, PFS, and OS, partial dates will be imputed as follows:

- If mmyyyy for the last contact known alive date = mmyyyy for the death date, then the death date will be set to the day after the last contact known alive date.
- If mmyyyy for the last contact known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB050465.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB050465 and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB050465 and is ongoing or ends during the course of study drug.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB050465. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

This is a Phase 2, multicenter, international, and open-label study. The study consists of 2 groups: Group A and Group B. In Group A, 100 subjects who were not previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. In Group B, up to 20 subjects who were previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. Data from Group A and Group B will be analyzed separately.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of INCB050465.

The full analysis set will be used for the summary of demographics, baseline characteristics, subject disposition, and analyses of all efficacy data.

5.3.2. Per Protocol Population

The PP population includes all subjects in the full analysis set who were compliant with the Protocol.

The following procedures will be performed to identify those subjects who are to be excluded from the PP population before the database freeze:

- Clinical review of Protocol deviations
- Clinical review of concomitant medications as defined in Section 5.6 of the Protocol
- Clinical review of the dose administration and drug accountability listing

The determination of subjects being considered for exclusion from the PP population by the clinical team will be prepared and signed before database freeze.

5.3.3. Safety Population

The safety population includes all subjects enrolled in the study who received at least 1 dose of INCB050465.

All safety analyses will be conducted using the safety population.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics and Baseline Disease Characteristics

The following demographics will be summarized and listed for the full analysis set: age, sex, race, ethnicity, weight, height, and BMI. ECOG performance status at baseline will be summarized and listed for the full analysis set.

6.1.2. Disease History

Time since diagnosis, initial disease type, time since transformation to DLBCL, stage at initial diagnosis, NCCN international prognostic index, current DLBCL subtype, current diagnosis type, current stage, presence of B-symptoms, and tumor markers will be summarized and listed for all subjects in the full analysis set.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (Day 1 date – date of diagnosis + 1) / 365.25.

Time since transformation to DLBCL will be calculated as follows:

Time since transformation (years) = (Day 1 date – date of transformation + 1) / 365.25.

6.1.3. Prior Cancer Therapy

Number of prior systemic cancer therapy regimens will be summarized for all subjects in the full analysis set. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. Number and percentage of subjects with each drug will be summarized by WHO drug class and WHO drug preferred term. Regimen name, component drugs, start and stop date, route of the medication, best response, reason for discontinuation, and date of relapse/progression will be listed.

Number of subjects who received prior radiation will be summarized for the full analysis set.

Number of subjects who had prior surgery or surgical procedure for cancer treatment will be summarized for the full analysis set. Date and description of the surgery/procedure will be listed.

Number of subjects who had prior hematopoietic stem cell transplant will be summarized for the full analysis set. Date of transplant, type of transplant, source of cells, line of therapy, best response, date of relapse/progression, and drug used with the transplant will be listed.

6.1.4. Medical History

Medical history will be coded to SOC and PT using MedDRA coding dictionary. For subjects in the full analysis set, medical history will be summarized by SOC and PT and listed.

6.2. Disposition of Subjects

The number and percentage of subjects who were treated, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized and listed for the full analysis set.

The number of subjects enrolled by country and site will also be provided for the full analysis set.

6.3. Protocol Deviations

Protocol deviations recorded on the CRF will be presented in the subject data listings.

6.4. Exposure

For subjects in the safety population, exposure to INCB050465 will be summarized descriptively as the following:

- **Duration of treatment with INCB050465 (days):** Date of last dose of study drug – date of first dose of study drug + 1.
- **Duration of treatment with INCB050465 for initial QD schedule (days):** Date of last dose of study drug during initial QD schedule – date of first dose of study drug + 1.
- **Duration of treatment with INCB050465 for QW schedule (weeks):** Ceiling of [(date of last dose of INCB050465 during QW schedule – date of first dose of INCB050465 during QW schedule + 1) / 7].
- **Average reported daily dose of INCB050465 for initial QD schedule (mg/day):** Total reported INCB050465 dose taken during initial QD schedule (mg) / duration of treatment with INCB050465 for initial QD schedule (days).

- **Average reported weekly dose of INCB050465 for QW schedule (mg/week):** Total reported INCB050465 dose taken during QW schedule (mg) / duration of treatment with INCB050465 for QW schedule (weeks).
- **INCB050465 dose modifications:** Number of subjects who had INCB050465 dose reduction and interruption will be summarized for initial QD schedule, QW schedule, and overall.

6.5. Study Drug Compliance

For subjects in the safety population, overall compliance (%) for INCB050465 will be calculated for all subjects as

compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the drug accountability CRF. If there is dispensed drug that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drug will be imputed by the dose taken as reported on the dosing CRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. Number and percentage of subjects in the safety population with each prior and concomitant medications will be summarized by WHO drug class and WHO drug preferred term.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Response Assessment

An objective assessment of disease status is required at baseline (screening) using the PET-CT–based response criteria of the Lugano Classification (Cheson et al 2014). Disease status will be subsequently assessed by PET-CT/MRI at Weeks 9, 18, 27, and every 18 weeks thereafter until disease progression.

Sites will use the PET-CT–based response criteria of the Lugano Classification to assess response to treatment locally. Positron emission tomography is required and therefore the criteria for PET-based response should be applied in most circumstances. Computed tomography/MRI–based response criteria are provided for those subjects with PET scans that

cannot be interpreted or who do not have FDG-avid disease. At each postbaseline disease assessment, response by PET will be collected in the eCRF as CMR, PMR, NMR, PMD, or NE; response by CT/MRI will be collected in the eCRF as CR, PR, SD, PD, or NE. Response by PET will be used as the overall response for the assessment if available, otherwise response by CT/MRI will be used as the overall response for the assessment.

All imaging (PET and CT or MRI) will be submitted to the IRC. Imaging data and applicable clinical data will be reviewed and response assessed using the PET-CT–based response criteria of the Lugano Classification (Cheson et al 2014) by independent reviewers as described in the Imaging Charter. At each postbaseline disease assessment, an overall timepoint response, the overall best response (including the date of first response, if applicable), and the overall date of progression (if applicable) for the subject, considering radiographic data and clinical data, will be provided by the oncologist (labeled with "ONCOLOGIST" in the data). These data will be used in the analyses of related response data.

7.2.2. Best Overall Response and Overall Response Rate

For responses by IRC, the best overall response for each subject will be provided by the oncologist.

For investigator-reported responses, the best overall response is the best response recorded before and including the first PD, in the order of CR/CMR, PR/PMR, SD/NMR, PD/PMD, and NE. In the case of SD/NMR, assessment must meet the SD/NMR criteria at least once on or after Day 49. Subjects who fail to meet this criterion will have best response of PD/PMD if the next available assessment after the initial assessment indicates PD/PMD or will have best response of NE if there are no additional assessments available.

A subject is considered a responder if they have a best overall response of CR/CMR or PR/PMR.

The ORR is the proportion of responders. Subjects who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR.

Best overall response as determined by the IRC will be summarized descriptively for subjects in Group A. The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated for subjects in Group A. Confidence intervals will be calculated based on the exact method for binomial distributions. This is considered the primary efficacy analysis of the study.

Best overall response as reported by the investigator will also be summarized descriptively for subjects in Group A. The ORR as reported by the investigator and its 95% exact binomial CIs will be calculated for subjects in Group A. Confidence intervals will be calculated based on the exact method for binomial distributions.

Response data as determined by IRC and those as reported by the investigator will be analyzed when all subjects have received at least 1 postbaseline disease assessment, or have progressed, withdrawn from the study, or died.

7.2.3. Subgroup Analyses for Overall Response Rate

Subgroups will be formed based on the following subject characteristics and baseline variables:

- Age: ≤ 65 years, > 65 years
- Gender: male, female
- Race: White, Others
- Geographic region: Europe, North America, Rest of World

Subgroups may be further divided or combined based on emerging data. The ORR as determined by IRC and its 95% CIs will be provided for subjects in Group A for each subgroup. A forest plot will be created to summarize the variability in ORRs as determined by IRC for subjects in Group A across subgroups.

7.3. Analysis of the Secondary Efficacy Parameters

7.3.1. Duration of Response

Duration of response is defined as the time from first documented evidence of CR/CMR or PR/PMR until disease progression or death due to any cause among subjects who achieve an overall response (ie, CR/CMR or PR/PMR) as determined by revised response criteria for lymphomas (Cheson et al 2014). For responses assessed by IRC, the date of first response and date of disease progression will be provided by the oncologist for subjects who have achieved best response of CR/CMR or PR/PMR. For investigator-reported response data, the date of PD will be the timepoint at which progression is first recorded. Censoring of DOR will follow the same algorithm as the censoring of PFS (Section 7.3.2).

The total number of responders as determined by the IRC, the number of subjects whose disease progressed as determined by the IRC or who died, and the number of subjects censored will be summarized for subjects in Group A. The Kaplan-Meier estimation of median DOR as determined by the IRC and its 95% CIs will be provided for subjects in Group A.

The total number of responders as reported by the investigator, the number of subjects whose disease progressed as reported by the investigator or who died, and the number of subjects censored will also be summarized for subjects in Group A. The Kaplan-Meier estimation of median DOR as reported by the investigator and its 95% CIs will be provided for subjects in Group A.

7.3.2. Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose of the study drug to the first documented disease progression as determined by revised response criteria for lymphomas (Cheson et al 2014), or death due to any cause, whichever occurs first. For responses assessed by the IRC, date of disease progression will be provided by the oncologist. For investigator-reported data, the date of PD will be the timepoint at which progression is first recorded. Censoring for PFS will follow the algorithm outlined in Table 1, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2007).

Table 1: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

NE = not evaluable; PD = progressive disease.

The number of subjects whose disease progressed as determined by the IRC or who died and the number of subjects censored will be summarized for subjects in Group A. The Kaplan-Meier estimation of median PFS as determined by the IRC and its 95% CIs will be provided for subjects in Group A.

The number of subjects whose disease progressed as reported by the investigator or who died and the number of subjects censored will also be summarized for subjects in Group A. The Kaplan-Meier estimation of median PFS as reported by the investigator and its 95% CIs will be provided for subjects in Group A.

7.3.3. Overall Survival

Overall survival is defined as the time from the date of first dose of study drug to death due to any cause. For subjects who are still alive at the time of the analysis, OS will be censored on the date the subject is last known to be alive.

The number of subjects who died and the number of subjects censored will be summarized for subjects in Group A. The Kaplan-Meier estimation of median OS and its 95% CIs will be provided for subjects in Group A.

7.3.4. Best Change in Target Lesion Size

For subjects with measurable lesions at baseline, target lesion sizes will be measured by sum of product of diameters. The best percentage change from baseline, defined as the largest decrease in target lesion sizes during the study, will be summarized, and a waterfall plot of the best percentage change will be generated for subjects in Group A using data from the IRC. Note that for subjects who only have increases in target lesion sizes from baseline, the smallest increase will be considered as the best change from baseline. For IRC, there will be 2 readers for each subject. The PET best response will be compared between the readers to determine whether an adjudicator is needed for the review. If there is no discordance, the results from the first radiology read (labeled with "RADIOLOGIST 1" in the data) will be used for the analysis. If there is discordance, an adjudication will be performed per the imaging Charter. The adjudicator will choose the read that he or she believes most accurately represents the PET best response. This is considered the "accepted read," and data from this reader will be used for the analysis. An indicator is provided to identify the read that is considered to be the accepted assessment in data from the IRC.

Best change in target lesion size as reported by the investigator will also be summarized. Target lesions considered "too small to measure" will be assigned a default value of 5 mm × 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event that a target lesion is unaccounted for in a particular postbaseline timepoint (ie, the assessment is missing or NE), then the overall sum of target lesions will not be evaluable for that postbaseline timepoint.

8. SAFETY AND TOLERABILITY

Sample data displays are provided in Appendix A.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few subjects.

Unless otherwise stated, all AEs reported on the CRF will be included in the summaries.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE version 4.03. The CTCAE reporting guidelines and grading details are available on the CTEP website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent. Therefore, a missing onset date will be considered treatment-emergent, with the following examples illustrating exceptions:

- If the stop/resolution date is before the first dose date on Day 1, then the AE will not be considered treatment-emergent.
- If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the AE will not be considered treatment-emergent.
- If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the AE will not be considered treatment-emergent.
- If only the day is missing, and the first day of the month is after the first dose date on Day 1, then the AE will be considered treatment-emergent.

8.2.2. Adverse Events of Special Interest or Adverse Events of Clinical Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities.

- ALT ≥ 5 × ULN
- AST ≥ 5 × ULN
- Colitis
- Diarrhea ≥ Grade 2
- Rash ≥ Grade 2
- Intestinal perforation
- Pneumonitis
- *Pneumocystis jirovecii* infection
- CMV infection
- Herpes simplex virus infection
- Varicella zoster virus infection
- Exfoliative dermatitis

The number of subjects who experienced any TEAEs of special interest will be summarized by maximum severity. Time to onset of new or worsening Grade 3 or 4 AEs will be summarized for ALT, AST, neutropenia, colitis, intestinal perforation, pneumonitis, *Pneumocystis jirovecii* infection, CMV infection, herpes simplex virus infection, varicella zoster virus infection, and exfoliative dermatitis. For rash and diarrhea events, time to onset of new or worsening Grade 2 or higher AEs will be summarized. ALT, AST, and neutropenia will be summarized based on the laboratory data.

8.2.3. Adverse Event Summaries

An overall summary of AEs will include:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any SAEs
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs
- Number (%) of subjects reporting any TEAEs related to INCB050465
- Number (%) of subjects reporting any SAEs related to INCB050465
- Number (%) of subjects reporting any Grade 3 or 4 AEs related to INCB050465
- Number (%) of subjects who temporarily interrupted INCB050465 because of TEAEs
- Number (%) of subjects who permanently discontinued INCB050465 because of TEAEs
- Number (%) of subjects with INCB050465 dose reductions because of TEAEs

- Number (%) of subjects who had a fatal TEAE
- Number (%) of subjects reporting any TEAEs during QW schedule
- Number (%) of subjects reporting any SAEs during QW schedule
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs during QW schedule
- Number (%) of subjects reporting any TEAEs related to INCB050465 during QW schedule
- Number (%) of subjects who temporarily interrupted INCB050465 because of TEAEs during QW schedule
- Number (%) of subjects who permanently discontinued INCB050465 because of TEAEs during QW schedule
- Number (%) of subjects with INCB050465 dose reductions because of TEAEs during QW schedule
- Number (%) of subjects who had a fatal TEAE during QW schedule

The following summaries will be produced by MedDRA term (if 10 or fewer subjects appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or 4 TEAEs by SOC and PT
- Summary of INCB050465 treatment-related AEs by SOC and PT
- Summary of INCB050465 treatment-related AEs by SOC, PT, and maximum severity
- Summary of Grade 3 or 4 INCB050465 treatment-related AEs by SOC and PT
- Summary of TEAEs leading to death by SOC and PT
- Summary of treatment-emergent SAEs by SOC and PT
- Summary of treatment-emergent SAEs by PT in decreasing order of frequency
- Summary of INCB050465 treatment-related SAEs by SOC and PT
- Summary of TEAEs leading to INCB050465 dose reduction by SOC and PT
- Summary of TEAEs leading to INCB050465 dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of INCB050465 by SOC and PT
- Summary of TEAEs during QW schedule by SOC and PT
- Summary of Grade 3 or 4 TEAEs during QW schedule by SOC and PT
- Summary of INCB050465 treatment-related AEs during QW schedule by SOC and PT

- Summary of TEAEs leading to death during QW schedule by SOC and PT
- Summary of treatment-emergent SAEs during QW schedule by SOC and PT
- Summary of INCB050465 treatment-related SAEs by SOC and PT
- Summary of TEAEs leading to INCB050465 dose reduction during QW schedule by SOC and PT
- Summary of TEAEs leading to INCB050465 dose interruption during QW schedule by SOC and PT
- Summary of TEAEs leading to discontinuation of INCB050465 during QW schedule by SOC and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, the value from the central laboratory has priority over the value from the local laboratory. Thereafter, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple laboratory nonmissing values for a subject's particular test at a scheduled visit, central laboratory values have higher priority over local laboratory values. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, line graphs will be provided for hemoglobin, platelet counts, WBC, neutrophils, and lymphocytes.

Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of subjects in the baseline category.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including weight, systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 2. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 2: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35ºC
Respiratory rate	> 24/min	< 12/min

8.5. Electrocardiograms

Twelve-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each subject during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of INCB050465.

Normal ranges for ECG values are defined in Table 3. Electrocardiogram values will be considered abnormal as well if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Subjects exhibiting ECG values outside the normal ranges will be listed with study visit and assigned treatment group. Abnormal values for subjects with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT and QTcF values, defined as absolute values > 450 msec or change from baseline > 30 msec, will be summarized.

Table 3: Normal Ranges for Electrocardiogram Values

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia's correction.

9. INTERIM ANALYSES

9.1. Overview of Interim Analyses

An interim futility analysis is planned when the first 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if ≤ 13 of the 40 subjects have responded (ie, CR/CMR or PR/PMR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment. [redacted] 20-subject cohort for which no formal futility analysis will be conducted.

An IDMC will be charged with evaluating interim futility results. The IDMC will consist of clinicians and an independent statistician. The IDMC will make recommendations to the sponsor at the planned interim futility analysis in Group A. The process by which the IDMC will make recommendations and decisions will be documented in the IDMC charter. Additional operational details of the interim analyses, including tables, figures, and listings provided to the DMC, will be provided in the DMC Charter.

9.2. Derivations and Calculations for Interim Analyses

The futility analysis will be conducted for exactly 40 subjects with stopping boundary as stated in Section 9.1. There is no efficacy interim analysis planned for the study.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 4.

Table 4: Statistical Analysis Plan Versions

SAP Version	Date
Original	22 MAR 2018

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf. Accessed December 20, 2017.

APPENDIX A. PLANNED TABLES AND FIGURES

This appendix provides a list of the planned tables and figures for the Clinical Study Report for Group A and Group B, unless otherwise specified. Outputs from Group A will have ".1" at the end of the numbering. Outputs from Group B will have ".2" at the end of the numbering. Standard tables will follow the conventions in the Standard Safety Tables initial version. Shells are provided for nonstandard tables. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list of tables, figures, and the shells are to be used as guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard	In-Text
Baseline and Demographic Characteristics				
1.1.1	Analysis Populations	FAS	X	X
1.1.2	Summary of Subject Disposition	FAS	X	X
1.1.3	Summary of Number of Subjects Enrolled by Country and Site	FAS	X	
1.2.1	Summary of Demographics and Baseline Disease Characteristics	FAS		X
1.3.1	Summary of Disease History	FAS		X
1.3.2	Summary of Prior Cancer Therapy	FAS		
1.3.3	Summary of Prior Systematic Cancer Therapy by WHO Drug Class and Preferred Term	FAS	X	
1.4.1	Summary of Prior Medications	FAS	X	
1.4.2	Summary of Concomitant Medications	FAS	X	
1.5.1	Summary of General Medical History	FAS	X	
Efficacy				
2.1.1	Summary of Best Overall Response and Overall Response Rate as Determined by IRC	FAS		X
2.1.2	Summary of Best Overall Response and Overall Response Rate as Reported by Investigator (Group A only)	FAS		X
2.1.3	Summary of Best Overall Response and Overall Response Rate as Determined by IRC by Subgroup (Group A only)	FAS		X
2.2.1	Summary of Duration of Response as Determined by IRC	FAS		X
2.2.2	Summary of Duration of Response as Reported by Investigator (Group A only)	FAS		X
2.2.3	Summary of Progression-Free Survival as Determined by IRC	FAS		X
2.2.4	Summary of Progression-Free Survival as Reported by Investigator (Group A only)	FAS		X
2.2.5	Summary of Overall Survival	FAS		X
2.2.6	Summary of Best Change in Target Lesion Size as Determined by IRC	FAS		X
2.2.7	Summary of Best Change in Target Lesion Size as Reported by Investigator	FAS		X

Table No.	Title	Population	Standard	In-Text
Safety				
3.1	Summary of Exposure and Compliance	Safety		X
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	
3.2.5	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.6	Summary of INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.7	Summary of INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	
3.2.8	Summary of Grade 3 or 4 INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.9	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.10	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.11	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.12	Summary of INCB050465 Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.13	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.14	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB050465 by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.16	Summary of Selected Treatment-Emergent Adverse Events of Special Interest by Highest Grade	Safety		X
3.2.17	Summary of Time to Onset of Selected Treatment-Emergent Adverse Events of Special Interest	Safety		X
3.2.18	Summary of Treatment-Emergent Adverse Events During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X

Table No.	Title	Population	Standard	In-Text
3.2.19	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.20	Summary of INCB050465 Treatment-Related Adverse Events During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.21	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.22	Summary of Serious Treatment-Emergent Adverse Events During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.23	Summary of INCB050465 Treatment-Related Serious Adverse Events During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.24	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Reduction During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.25	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Interruption During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.26	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB050465 During QW Schedule by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.3.1	Summary of Laboratory Values - Hematology	Safety	X	
3.3.2	Shift Summary of Hematology Laboratory Values in CTC Grade - To the Worst Abnormal Value	Safety	X	X
3.3.5	Summary of Laboratory Values - Chemistry	Safety	X	
3.3.6	Shift Summary of Chemistry Laboratory Values in CTC Grade - To the Worst Abnormal Value	Safety	X	X
3.4.1	Summary of Systolic Blood Pressure	Safety	X	
3.4.2	Summary of Diastolic Blood Pressure	Safety	X	
3.4.3	Summary of Pulse	Safety	X	
3.4.4	Summary of Respiration Rate	Safety	X	
3.4.5	Summary of Body Temperature	Safety	X	
3.4.6	Summary of Weight	Safety	X	
3.5.1	Summary of PR Interval (msec) From 12-Lead ECG	Safety	X	
3.5.2	Summary of RR Interval (msec) From 12-Lead ECG	Safety	X	
3.5.3	Summary of QT Interval (msec) From 12-Lead ECG	Safety	X	
3.5.4	Summary of QRS Interval (msec) From 12-Lead ECG	Safety	X	
3.5.5	Summary of QTcF Interval (msec) From 12-Lead ECG	Safety	X	
3.5.6	Summary of Outliers of QT and QTcF Interval Values From 12-Lead ECG	Safety	X	X

Figures

Figure No.	Title
4.1.1	Forest Plot of Overall Response Rate as Determined by IRC (Group A only)
4.2.1	Kaplan-Meier Estimates of Duration of Response as Determined by IRC
4.2.2	Kaplan-Meier Estimates of Duration of Response as Reported by Investigator (Group A only)
4.2.3	Kaplan-Meier Estimates of Progression-Free Survival as Determined by IRC
4.2.4	Kaplan-Meier Estimates of Progression-Free Survival as Reported by Investigator (Group A only)
4.2.5	Kaplan-Meier Estimates of Overall Survival
4.2.6	Waterfall Plot of Best Percentage Change in Sum of Target Lesions as Determined by IRC
4.6	Line Graph of Mean Values Over Time for Selected Laboratory Values (Hemoglobin, Platelet Counts, WBC, Neutrophils, and Lymphocytes)

Listings

Listing No.	Title
2.1.1	Subject Enrollment and Disposition Status
2.1.2	Subject Inclusion and Exclusion Criteria Violations
2.2	Protocol Deviations
2.3	Analysis Population
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2	Disease History
2.4.3	Prior Systemic Therapy
2.4.4	Prior Surgery or Surgical Procedure
2.4.5	Prior Stem Cell Transplant
2.4.6	Medical History
2.4.7	Prior and Concomitant Medication
2.5.1	Study Drug Compliance
2.6.1	Best Overall Response, Duration of Response, and Progression-Free Survival per IRC
2.6.2	Best Overall Response, Duration of Response, and Progression-Free Survival per Investigator (Group A only)
2.6.3	Overall Response Assessment by Visit per IRC
2.6.4	IRC Response Assessment: Target Lesions
2.6.5	IRC Response Assessment: Non-target Lesions
2.6.6	IRC Response Assessment: New Lesions
2.6.7	Overall Response Assessment by Visit per Investigator
2.6.8	Investigator Response Assessment: Target Lesions
2.6.9	Investigator Response Assessment: Non-target Lesions
2.6.10	Investigator Response Assessment: New Lesions
2.6.11	Deaths and Overall Survival
2.7.1	Study Drug Administration
2.7.2	Adverse Events
2.7.3	Serious Adverse Events
2.7.4	Grade 3 and 4 Adverse Events
2.7.5	Fatal Adverse Events
2.7.6	Treatment-Related Adverse Events
2.7.7	Adverse Events Leading to Interruption, Reduction or Discontinuation of INCB050465

Listing No.	Title
2.8.1	Clinical Laboratory Values - Hematology
2.8.2	Clinical Laboratory Values - Chemistry
2.8.3	Abnormal Clinical Laboratory Values - Hematology
2.8.4	Abnormal Clinical Laboratory Values - Chemistry
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values

Signature Manifest

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